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APPLICATION FOR A PATENT
IN FRANCE

No.: 98-00009

Filed on: January 5, 1998

With the following claimed filing priority: *[blank]*

In the name of: OPTISINVEST

Title: **DEVICE FOR INTRAOCULAR TRANSFER OF ACTIVE PRODUCTS BY IONTOPHORESIS**

DEVICE FOR INTRAOCULAR TRANSFER OF ACTIVE PRODUCTS BY IONTOPHORESIS

The present invention relates to a device for intraocular transfer of active products by iontophoresis.

Iontophoresis is a technique that was proposed as early as 1747 by Verrati. It consists of the administration, specifically of medications, into the body through the tissues with the aid of an electrical field that uses a slight difference in potential. The active electrode, which is in contact with the medication, is placed on the area to be treated, while a second electrode, whose purpose is to close the electrical circuit, is located elsewhere on the body.

The electrical field facilitates the migration of the active products, which are preferably ionized. This technique is currently being utilized in the treatment of skin diseases, and various devices intended for this purpose are commercially available.

The application of iontophoresis to treatment of the eye has been the subject of numerous animal experiments and several clinical trials, with the aid of various devices.

Known devices use a pad soaked with a solution that contains a medication and that is in contact with the surface of the cornea and the sclera. Other devices use a cupule or a pipette. For example, a device using a cupule is described in United States patent No. 4,564,016 (David M. Maurice). With this device, the medication is administered in a quasi-punctural manner through the sclera.

Generally speaking, the authors reported inferior reproducibility of their results, which they attributed either to the presence of differences between the animals tested or to unexplained biological phenomena. Moreover, certain operating techniques involved the use of an active electrode having a very small surface area and a very high current density, which increases the risk of damage to the tissues, up to and including burns. This is the case in particular with the device described in the above-mentioned U.S. patent No. 4,564,016, which recommends a current density of at least 50 mA/cm^2, which can even be as high as 2,000 mA/cm^2.

Some experiments were performed with alkaline solutions whose high pH had the effect of causing local tissue damage. For example, the article by T.T. Lam et al. entitled "Intravitreal delivery of gancyclovir in rabbits by transscleral iontophoresis," as published in the *Journal of Ocular Pharmacology* (Vol. 10, Part 3 (1994), pp. 571-575), describes the punctual administration of a solution whose pH of 10.8 cannot be envisioned under non-laboratory conditions.

The article by F. Behar-Cohen et al. entitled "Iontophoresis of dexamethasone in the treatment of endotoxin-induced uvetis in rats," which appeared in the *Review of Experimental Eye Research* (Vol. 1997-65 (October 1997), pp. 533-545), involves transcorneoscleral iontophoresis performed on rats, for the treatment of uveitis, i.e., a pathology that affects the uvea. In this technique, the medication is diffused essentially through the cornea, and is then diffused into the ocular media.

In practice, because of the scant reproducibility of the experimental findings usually obtained, and, above all, the description of burns and tissue necrosis at the application site of the iontophoresis device, transocular iontophoresis has remained in the laboratory stage and is still not recognized as a patient treatment method.

The invention relates to a device for transferring at least one active product into the eyeball by iontophoresis, so as to allow outpatient treatments to be performed reproducibly.

Therefore, the invention relates to a device for transferring at least one active product into the eyeball by iontophoresis, which device includes a reservoir for the active product, specifically a medicine, into the eyeball by iontophoresis, including a reservoir for the active product, which reservoir can be applied to the eye of a patient; at least one active surface electrode located in the reservoir; a passive electrode; and a current generator, characterized in that a so-called "active" electrode is a surface electrode positioned facing the ocular tissues located at the periphery of the cornea. The areas of the eyeball facing the electrode are the corneoscleral limbus, the conjunctiva and/or the sclera and/or the ciliary body and/or the root of the iris and/or the *pars plana* and/or the anterior vitreous, and/or the non-detachable, non-functional retina.

Inasmuch as the transfer takes place through one or more ocular tissues located at the periphery of the cornea over a broad application surface, reproducibility, the homogeneity of the transfer, and effectiveness are all increased. These tissues are impregnated with the medication (or active product), which can even be concentrated there, while the concentrations in the ocular

media remain low. These concentrations do not reflect the concentrations of the intratissular medication. Thus, the medication is not rapidly eliminated by the renewal of the ocular fluids (i.e., the aqueous humor (AH) and the vitreous (V).

Moreover, inasmuch as the active product is not in contact with the cornea, the disadvantages of transcorneal iontophoresis and the risk of endothelial lesions (i.e., the presence of vision problems after the procedure, linked to either endothelial lesions or temporary epithelial lesions, or to temporary depositions of active products), which are manifested as blurred vision. Thus, the treatment is truly ambulatory.

Lastly, because the treatment is applied to a ring-shaped area peripheral to the cornea, a central cylindrical region of the device may be completely open, so that the practitioner can control visually the centered position of the device during iontophoresis.

All of the ocular tissues may be treated, i.e., the conjunctiva, cornea, sclera, iris, lens, ciliary body, choroid, retina, and optic nerve.

Depending on the parameter selected for the current (current intensity and duration of treatment), certain tissues may be targeted more specifically.

For an adult (nominal corneal diameter: 12 mm), the annular electrode or the electrodes in the form of annular sectors (as obtained, for example, through electrodeposition) may have an inside diameter of 12.5 mm to 14 mm, and an outside diameter of 17 mm to 22 mm, which corresponds to a surface area of approximately 75 mm^2 to 250 mm^2, and preferably from 17 mm to 20 mm. The maximum diameter is selected such that the functional retina is not reached. The dimensions must be adapted proportionally for a child whose eye has not reached adult size. In other words, and generally speaking, the inside diameter of the annular electrode or electrodes is greater than the diameter D of the cornea and less than or equal to 1.2D, and the outside diameter of the annular electrode or electrodes is greater than or equal to 1.4D and less than or equal to 1.8D, and preferably less than or equal to 1.7D.

The current generator may consist of a generator that generates direct current [DC] whose nominal density is less than 10 mA/cm^2, and that includes a control device that allows the said direct current to be applied for a period ranging from 30 seconds to 10 minutes, and specifically from 1 minute to 10 minutes.

The density of the said current is advantageously adjustable between 0.1 mA/cm^2 and 5 mA/cm^2, for example, between 0.2 mA/cm^2 and 5 mA/cm^2, or else between 0.8 mA/cm^2 and 5 mA/cm^2.

The current may be applied gradually, for example, during the first few seconds, thereby avoiding the patient's muscular reflex reactions.

The current is advantageous supplied at a voltage between 1.5V and 9V, and preferably between 2V and 8V.

The active product may be present in any concentration. Specifically, it should be less than or equal to the saturation concentration of the active product in water. It is preferably greater than or equal to a threshold concentration starting at which an accumulation occurs in certain ocular tissues, followed by a distribution to other tissues.

The pH of the active product placed in the reservoir is advantageously between 6 and 8, and preferably between 7 and 7.6. It should be noted that because the active product is not in contact with the cornea, the pH may be higher than the values indicated above, because the conjunctiva and the sclera are less sensitive (in terms of both sensitivity and lesions) to pH values that are slightly acidic or basic. The cornea should remain transparent. Any change in physiological conditions presents the risk of changing its tissular characteristics and therefore its transparency. The conjunctiva is a mucous membrane, and the sclera is a connective tissue. These two tissues are very strong, and their function (in the treatment application area) is not directly involved in the transmission of photons to the retina. These are supporting tissues.

The device preferably includes a pumping device which ensures the circulation of an active product, such as a medication solution, inside the reservoir. On the one hand, such a pumping device makes it possible to eliminate the gas bubbles that can form during iontophoresis, and, on the other hand, it allows the composition and pH of the solution to be kept essentially constant during treatment, thereby improving its reproducibility.

In a first embodiment, the device has an annular reservoir that has an annular electrode, which may define the bottom of the reservoir.

In a second embodiment, the device has an annular reservoir that has a plurality of compartments, in the form of annular sectors, and electrodes in the form of annular sectors, which may define the bottom of the annular sectors.

In a third embodiment, the device consists of a corneal lens which is provided, on its inner surface, with a surface electrode, and which contains a gel that contains at least one active product, or which itself has a spongy structure (for example, a reticulated matrix) and contains the active product.

The device preferably includes, on an outer surface, a passive electrode that comes into contact with the patient's partially closed eyelid, which keeps the device in place throughout the duration of the treatment. This arrangement also has the advantage of providing an improved electrical contact, because it involves an aqueous medium.

Other characteristics and advantages of the invention will be more clearly understood through a reading of the following description, which is offered as a non-limitative example, in conjunction with the attached drawings, on which:

- Figures 1a and 1b represent, respectively, a cross-sectional view and a top view of an example of the device described in the above-mentioned article by F. Behar-Cohen et al.;

- Figures 2a and 2b represent, respectively, a cross-sectional view and a top view of an example of the device according to the invention;

- Figures 3a, 3b, and 3c represent, respectively, a cross-sectional view, a top view, and a perspective view of a device according to the invention that allows the administration of three active products (for example, three medications);

- Figure 4 represents a cross-sectional view of a variant of the device shown in figures 3a through 3c;

- Figures 5a and 5b represent a device according to the invention, in the form of a meniscus intended for the administration of three active products (for example, three medications), in gel form;

– Figures 6a through 6c represent, respectively, a perspective view, a cross-sectional view, and a partial cross-sectional view of a meniscus device according to the invention;

– Figure 7 represents a preferred embodiment of a device intended for the administration of active products (for example, medications);

– Figures 8a and 8b show the results of a test performed on rabbits, with the concentration in μg/mg of dry tissue and in μg/ml for the ocular media on the ordinate, and the time (in hours) on the abscissa; and

– Figure 9 represents a device according to the invention, placed on an eye to be treated.

Figure 1 represents schematically the iontophoresis system implemented in the above-mentioned article by F. Behar-Cohen et al. It includes a reservoir [8] made of polymethyl methacrylate (PMMA) defined by a cylindrical wall [2] and a bottom [3], in proximity to which is provided a circular electrode [4] made of platinum. The reservoir [8], which is 6 mm in diameter, covers the cornea, the limbus, and the first millimeter of the sclera of a rat. An input tube [5] allows the reservoir [8] to be filled with a solution containing 1 mg of dexamethasone per ml of a sterile saline solution having a pH of 7, and a discharge tube [6] allows the removal of the air bubbles that form during iontophoresis. Continuous circulation of the solution allows the pH of the solution in contact with the cornea to be kept constant.

A return electrode [7] is placed in contact with one of the rat's paws.

The system also includes a voltage source [VS] and a current regulator [I]. An impedance measurement device [IMM] allows the detection of any electrical discontinuity, and triggers an alarm [A]. The charge quantity delivered is displayed on the generator at the end of treatment, and ensures the reproducibility of the treatment as administered.

Experiments have been performed with a current of 400 μA for 4 minutes, i.e., a density of 1.2 mA/cm^2 and a total charge of 0.12 coulombs, i.e., 0.4 C/cm^2.

The device according to the invention, in a preferred embodiment as shown in figures 2a and 2b, allows the transfer of an active product (for example, a medication) essentially through at least one ocular tissue.

The active electrode is advantageously placed at a distance a from the surface of the patient's eye, which distance is sufficient to avoid a short-circuit or to avoid accidental contact with the eye. This distance a is preferably equal to at least 4 mm.

The device may be made of PMMA or, preferably, of silicone (for example, PDMS [polydimethyl siloxane] with a Shore hardness of 20), for better leakproofness at the point of contact with the eye.

The device [10] has an annular wall [17] and two cylindrical lateral walls (an inner wall [19] and an outer wall [18]) that define an annular region [15] that forms a reservoir for an active solution (such as a medication solution) to be administered by iontophoresis to the periphery of the cornea [C] of an eye [20] to be treated. The extremity of the wall [18] facing the wall [17] rests, by means of a tapered region [19'], on the edge of the cornea [C], such that only an area that is peripheral to the cornea [C] and that includes one or more ocular tissues is bathed by the medication solution contained in the reservoir [15]. An active annular electrode adjoins the wall [17]. Two conductive connections [11'] and [12'] allow the active electrode [11] and the return electrode [12] (which is advantageously located on the outer surface of a ring [16]) to be connected electrically, so that the patient's partially closed eyelid can come into contact with the electrode [12] and thereby close the circuit.

Alternatively, the return electrode may be separated and placed on the patient's forehead, near the eye to be treated.

Openings [13] and [14] in the wall [17] allow the reservoir [15] to be filled, and/or also allow the circulation of the medication solution.

The flat annular electrode [11] preferably covers the entire surface of the wall [17] that defines the bottom of the annular reservoir [15]. Naturally, partial coverage may also be envisioned, but it can only have an unfavorable effect on the effectiveness of the treatment. In any event, the reservoir [15] should not cover any part of the cornea [C]. .

The device shown in figures 3a, 3b, and 3c allows the administration of several (in this case, three) active products (for example, medications) in liquid or gel form, each of which is placed in one of the three cavities [45] [46] [47] in the form of an annular sector, each of which has an active electrode [41] [42] [43], respectively. The device has an annular wall [27] and two cylindrical walls (an inner wall [49] and an outer wall [48]), and the sectors are defined by

separator walls [40]. This device is placed on the patient's eye in the same way as the device shown in figures 2a and 2b. Conductive connections [41'] [42'] [43'] pass through the wall [27] in order to supply electricity to the active electrodes [41] [42] [43].

The device shown in Figure 4 is distinguished by the presence of liquid-circulation tubes that are present for each cavity [45] [46] [47]. The drawing shows the tubes [84] [85] and [86] [87] that correspond to the cavities [45] and [46].

The device shown in figures 5a and 5b is a meniscus in the form of a ring. It has three reservoirs [55] [56] [57], each of which is intended to receive a medical gel or a porous material, such as a sponge, impregnated with an active product (for example, a medication). An active electrode [51] [52] [53] is associated with each reservoir, respectively. The reservoirs [55] in the form of sectors are defined by separator walls [50].

The device shown in figures 6a and 6b is a ring-shaped flat meniscus. It is made of a material that may be the same material that contact lenses are made of. The cylindrical central space [63] is open, and (as in the other models) allows visual control of the centered position of the device. An electrode [61] (which may be created, for example, by electrodeposition) covers the slightly concave inner surface [63] of the bottom of the annular cavity [62]. A return electrode [64] (which may be created, for example, by electrodeposition) covers the periphery of the convex outer surface [66] of the bottom of the annular cavity [62], so as to allow an electrical return contact through at least one of the closed eyelids [22] [24] of the patient. The path of the electrical contact wires [67] [68] is designed to allow the wires to exit between the eyelids.

Generally speaking, the device according to the invention is suitable for use with simple molecules or with groups of molecules used as an active product (for example, medications and/or peptides and/or proteins and/or gene fragments) and whose molecular weight is less than 100 kilodaltons.

The direct current that is used is constant, and is regulated to a current density not exceeding 10 mA/cm^2. This current density is advantageously adjustable between 0.1 mA/cm^2 and 5 mA/cm^2, and, for example, between 0.2 mA/cm^2 and 5 mA/cm^2. The preferred value range is between 0.8 mA/cm^2 and 5 mA/cm^2. The duration of treatment may be between 30 seconds and 10 minutes. Specifically, it may be between 1 minute and 10 minutes.

For human beings, the diameter of the cornea (with the limbus) is approximately 12 to 13 mm, with an *ora serrata* approximately 18 mm in diameter.

For example, the treatment of adults may involve the use of an annular electrode (or several electrodes in the form of annular sectors) whose inside diameter is between 12.5 mm and 14 mm, and whose outside diameter is between 17 mm and 22 mm, and preferably between 17 mm and 20 mm, which corresponds to a surface area of approximately 75 mm^2 to 250 mm^2, and preferably from 17 mm to 20 mm. In this case, the current may, for example, be 400 μA, and may be applied for 4 minutes.

It should be noted that the placement of the active electrodes (that is, the surface electrodes positioned facing the area(s) to be treated allows the associate of direct current with a current density which itself is constant and homogeneous over the entire surface of the area to be treated.

This arrangement has several advantages. Firstly, the current density is prevented from reaching locally high values in certain parts of the area to be treated and thereby causing undesirable side effects. Secondly, because of the homogeneity of the current density in the area to be treated, the penetration of the active product(s) (for example, medications) is also homogeneous over the area to be treated.

Under no circumstances is the electrode positioned opposite the functional retina.

Within the scope of the present invention, the administration of at least one active product (for example, a medication) is achieved through the tissues that allow better penetration of the active product into the anterior and posterior segment, i.e., the corneoscleral limbus, the conjunctiva, the sclera, the ciliary body, the root of the iris, the *pars plana*, the anterior vitreous, the choroid, and the non-detachable, non-functional retina.

The lack of contact with the cornea avoids any risk of physical or chemical lesions, or, specifically, temporary or permanent ocular problems arising from treatment. This lack of contact also allows a central space to be kept open, thereby allowing the practitioner to control the position of the device throughout the treatment.

Moreover, it has been noted that, starting with a given concentration of the active product (which varies depending on the nature of the active product), the active product accumulates in certain tissues of the eye (e.g., the space under the tendon, the sclera, and the suprachoroidal

space, and, to a lesser extent, in the iris [I] and the ciliary body [CC]) before being distributed gradually to other tissues (e.g., the choroid [CH] and the retina [RET]), thereby increasing the duration of the effect (i.e., the half-life before elimination of the active product).

This phenomenon is illustrated by the attached graphs (figures 8a and 8b), which were obtained through experiments performed on rabbits with methylprednisone hemisuccinate (150 mg/ml, 2 mA). The distribution effect was not observed with a solution at 62.5 mg/ml. The concentration threshold that allows distribution is approximately 100 mg/ml.

The device according to the invention may consist of a body of revolution. However, it is preferably essentially oval, in order to take into consideration the presence of the eyelids, on the one hand, and the slightly oval profile of the cornea, on the other hand.

The device shown in Figure 7 has a cavity with an elliptical outer profile, whose focal axis (parallel to the eyelid closure line) is 20 mm long and whose lesser axis is 18 mm long.

An elliptical inner profile of the treatment cavity may, for example, have a greater axis (parallel to the eyelid closure line) that is 13.5 mm long, and a lesser axis (perpendicular to this line) that is 12.5 mm long.

The device shown in Figure 7 has four cavities [71] [72] [73] [74], each of which has an active electrode [75] [76] [77] [78] that is supplied with electricity by an individual electrical circuit [79] [80] [81][82], analogous to the arrangement shown in Figure 1, which forms an integral part of the device. The electrical circuits are powered by a battery [84] that constitutes the voltage generator [VS] and includes a DC power source [I] adjusted to a selected value, and a timer [T] that allows the desired treatment time to be set. Alternatively, the group of circuits may be placed on a single integrated circuit, or else the functions may be distributed among several internal circuits connected by a bus [85].

CLAIMS

1. Device for transferring at least one active product into the eyeball by iontophoresis, including a reservoir that contains the active product and that can be applied to the eye of a patient; at least one active electrode located in the reservoir; a passive electrode; and a current generator, characterized in that a so-called "active" electrode is a surface electrode [11] [41] [42] [43] [51] [53] [61] positioned facing at least one ocular tissue located at the periphery of the cornea.

2. Device according to Claim 1, characterized in that the current generator generates a direct current [DC] whose nominal density is less than 10 mA/cm^2, and in that it includes a control device that allows the said direct current to be applied for a period ranging from 30 seconds to 10 minutes, and specifically from 1 minute to 10 minutes.

3. Device according to Claim 2, characterized in that the said current density is between 0.1 mA/cm^2 and 5 mA/cm^2.

4. Device according to Claim 3, characterized in that the said current density is between 0.2 mA/cm^2 and 5 mA/cm^2, and specifically between 0.8 mA/cm^2 and 5 mA/cm^2.

5. Device according to any one of the foregoing claims, characterized in that the reservoir [15] [45] [46] [47] [55] [56] [57] and/or the active electrode [11] [41] [42] [43] [51] [52] [53] is annular.

6. Device according to any one of the foregoing claims, characterized in that the reservoir [15] [45] [46] [47] [55] [56] [57] [71] [72] [73] [74] [62] has an inside diameter di with $D < di \leq 2D$, where D indicates the diameter of the cornea, and an outside diameter de with $1.4D \leq de \leq 1.8D$, and preferably $1.4D \leq de \leq 1.7D$.

7. Device according to Claim 6, characterized in that the inside diameter di is between 12.5 mm and 14 mm, and in that the outside diameter de is between 17 mm and 22 mm, and preferably between 17 mm and 20 mm.

8. Device according to any one of the foregoing claims, characterized in that the said current is supplied at a voltage between 1.5V and 9V, and specifically between 2V and 8V.

9. Device according to any one of the foregoing claims, characterized in that the pH of the said active product placed in the reservoir [15] [45] [46] [47] [55] [56] [57] [71] [72] [73] [74] [62] is between 6 and 8, and preferably between 7 and 7.6.

10. Device according to any one of the foregoing claims, characterized in that the said device includes a pumping device which ensures the circulation of a medication solution inside the reservoir.

11. Device according to any one of the foregoing claims, characterized in that the device has an annular reservoir having a plurality of compartments [45] [46] [47] [55] [56] [57] [71] [72] [73] [74] in the form of annular sectors, and electrodes [41] [42] [43] [51] [52] [53] [75] [76] [77] [78] in the form of annular sectors.

12. Device according to any one of the foregoing claims, characterized in that the device has an annular reservoir which has an annular compartment [15] [62] and an annular electrode [11] [61].

13. Device according to any one of the foregoing claims, characterized in that the said reservoir [15] [45] [46] [47] [55] [56] [57] has an elongated form, such as an elliptical form.

14. Device according to any one of the foregoing claims, characterized in that the said reservoir [45] [46] [47] [55] [56] [57] [62] contains at least one gel or one porous material such as a sponge, impregnated with an active product.

15. Device according to any one of claims 11 to 14, characterized in that the device is a flat meniscus.

16. Device according to any one of the foregoing claims, characterized in that the device includes, on an exterior surface, a passive electrode [12] [44] [64], which comes into contact with the inner surface of the patient's eyelid, which is at least partially closed and which keeps the device in place throughout the duration of the treatment.

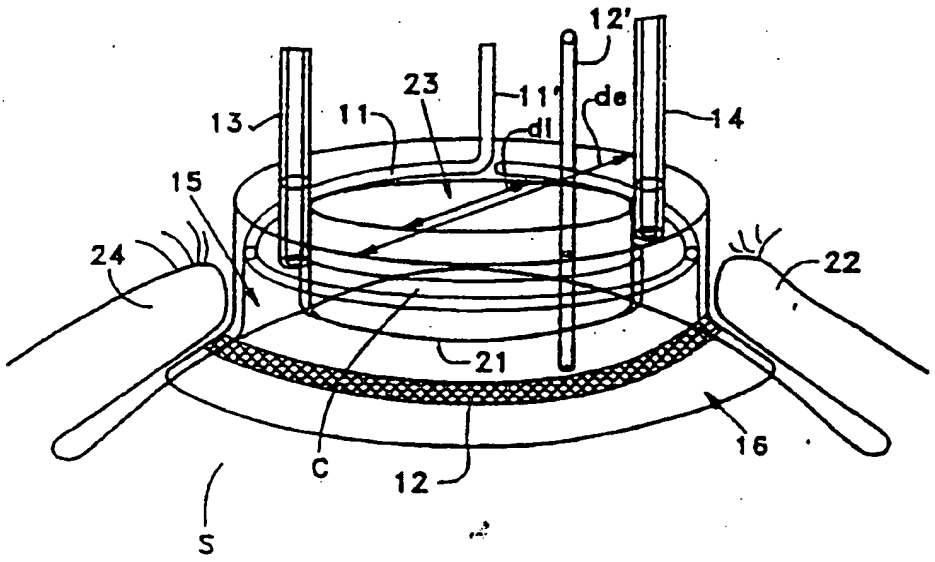
F1217/1FR

DEVICE FOR INTRAOCULAR TRANSFER OF ACTIVE PRODUCTS BY IONTOPHORESIS

DESCRIPTIVE ABSTRACT

The invention relates to a device for transferring at least one active product, specifically a medication, into the eyeball by iontophoresis, including a reservoir [15] that contains the active product and that can be applied to the eye of a patient. The reservoir [15] has at least one active surface electrode [11] positioned facing an ocular tissue located at the periphery of the cornea (C), a return electrode [12], and a current generator.

The return electrode [12] is preferably in contact with the partially closed eyelids [22] [24] of the patient.



[Figure 2c]

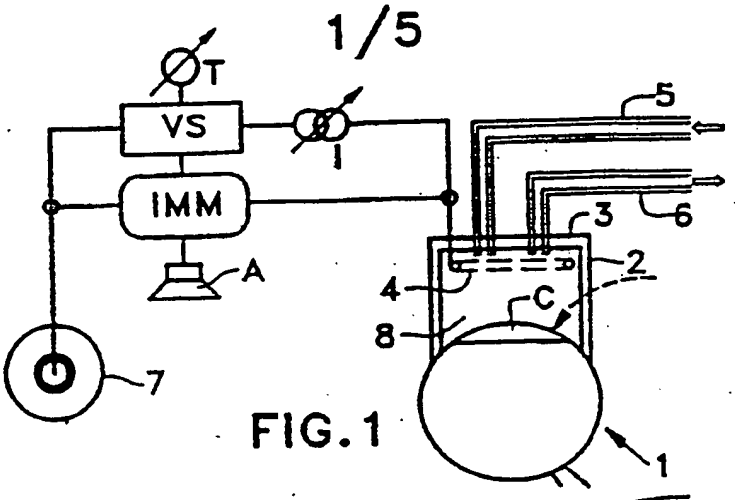


FIG.1

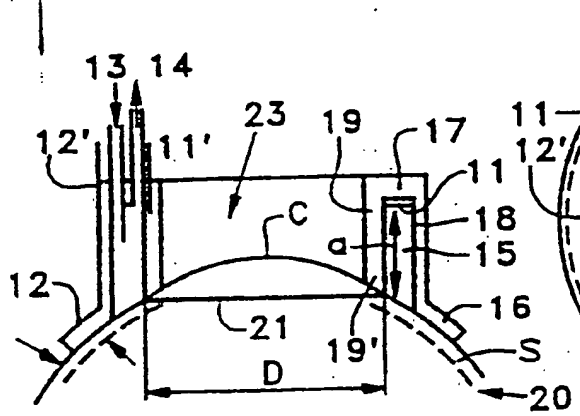


FIG.2a

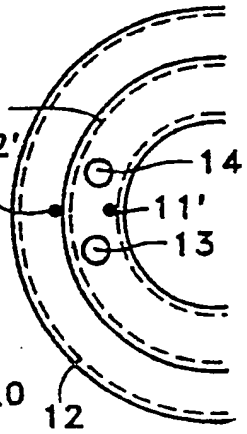


FIG.2b

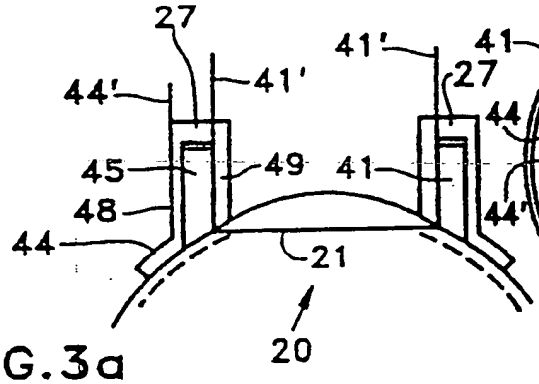


FIG.3a

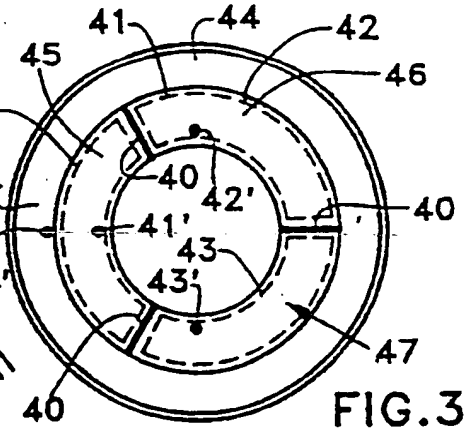


FIG.3b

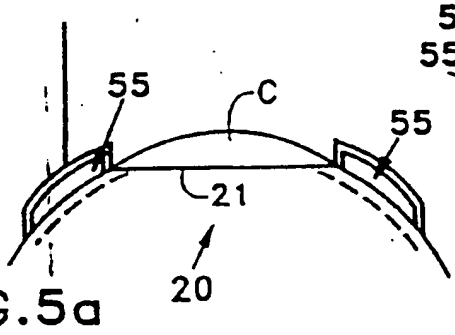


FIG.5a

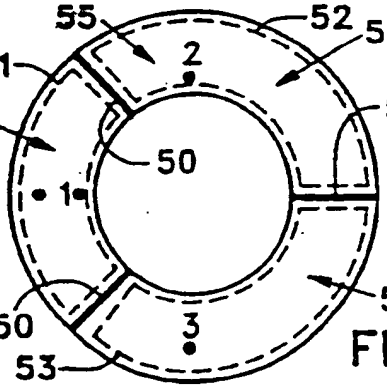


FIG.5b

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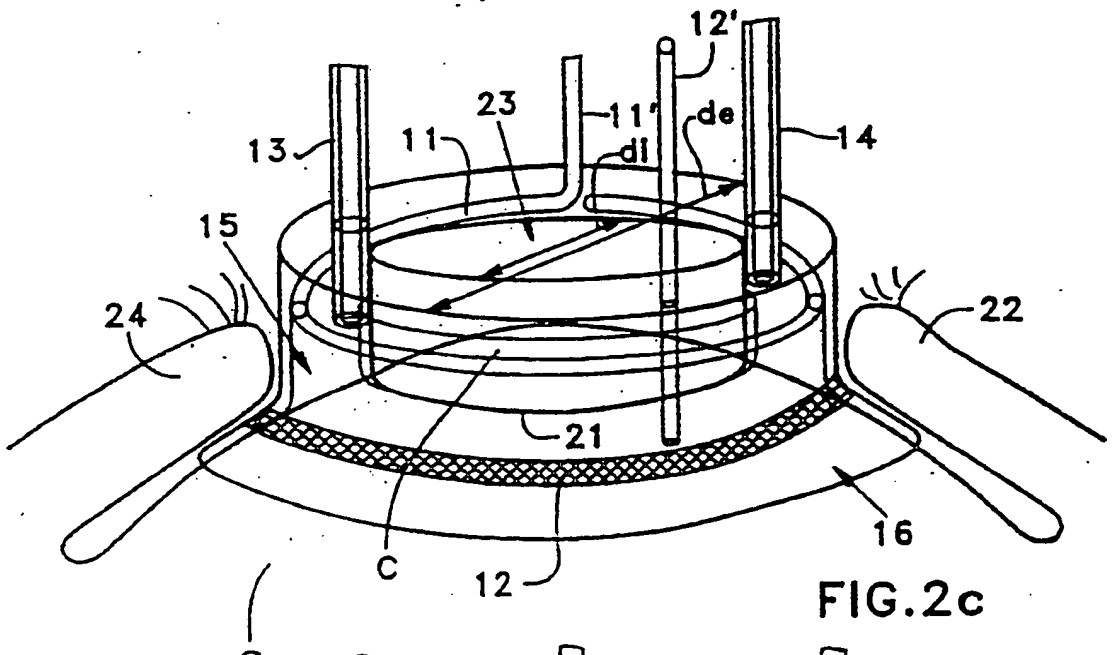


FIG.2c

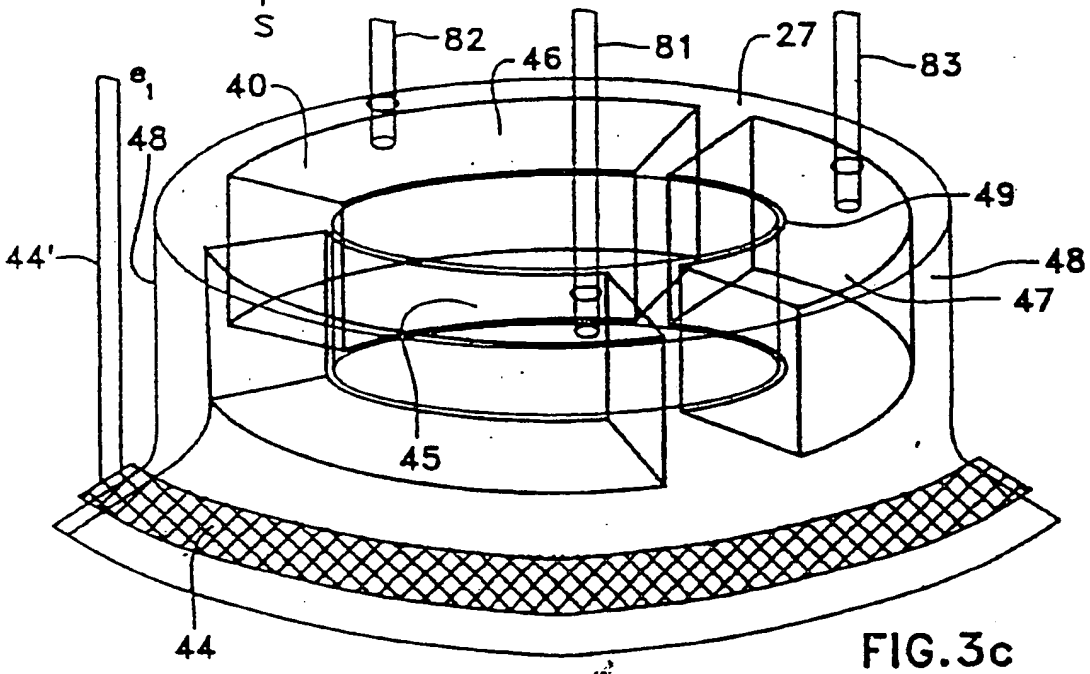


FIG.3c

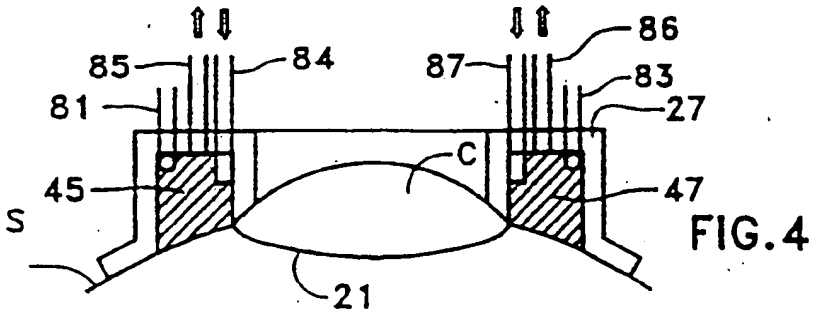


FIG.4

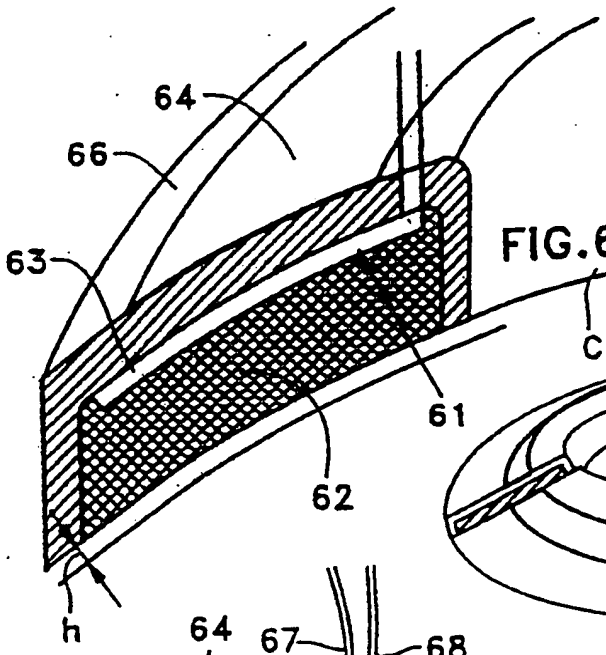


FIG.6c

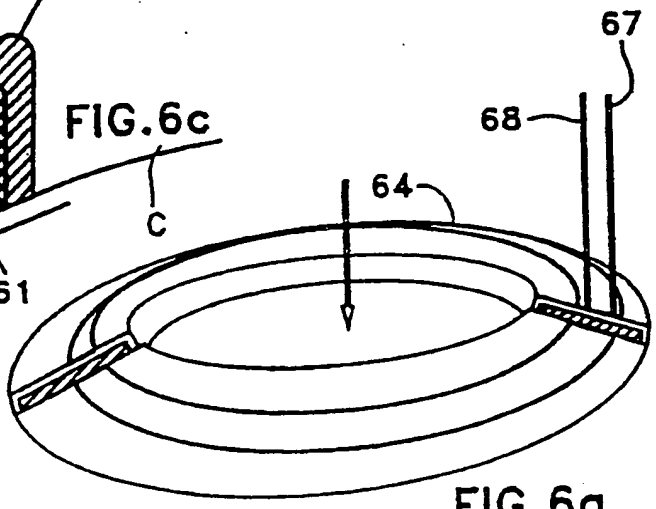


FIG.6a

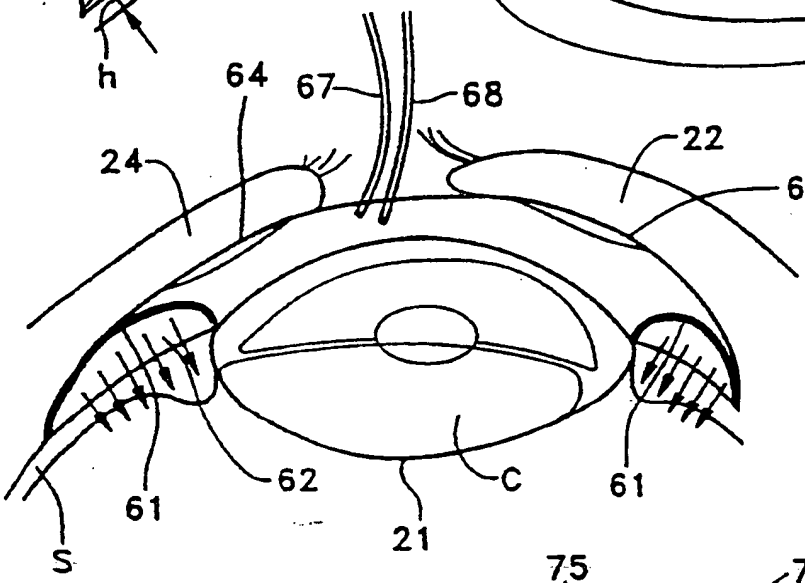


FIG.6b

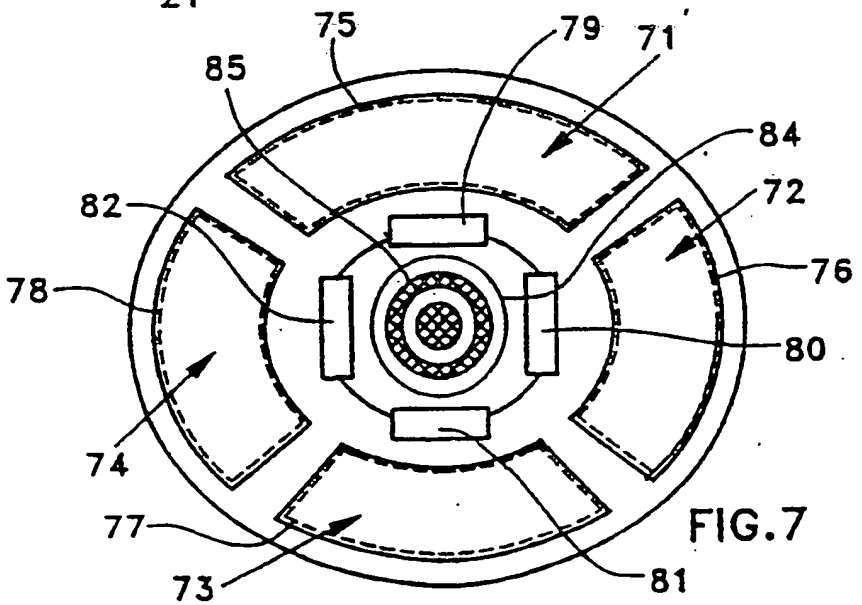
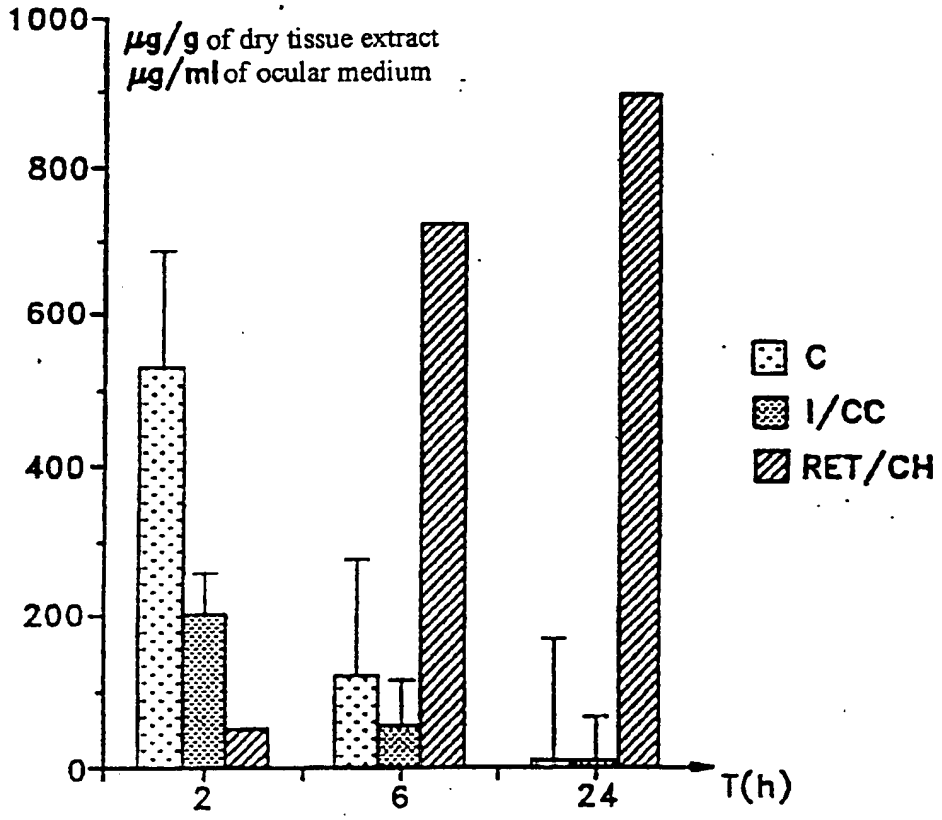


FIG.7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800
600
400
200
0
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µg/ml of ocular medium
C
I/CC
RET/CH
2
6
24
T(h)

FIG.8a

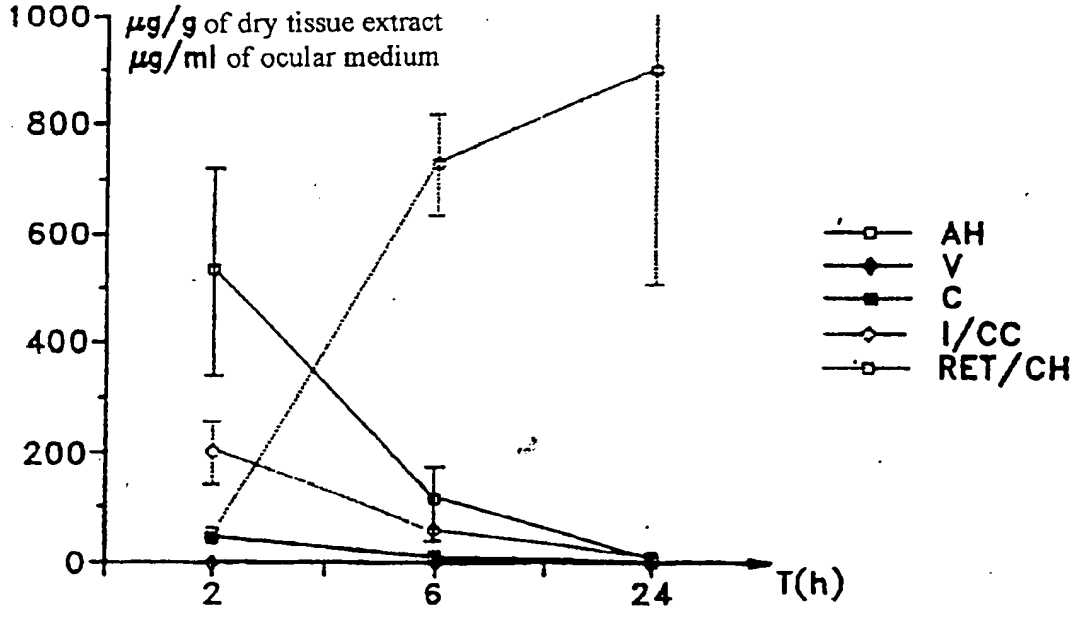
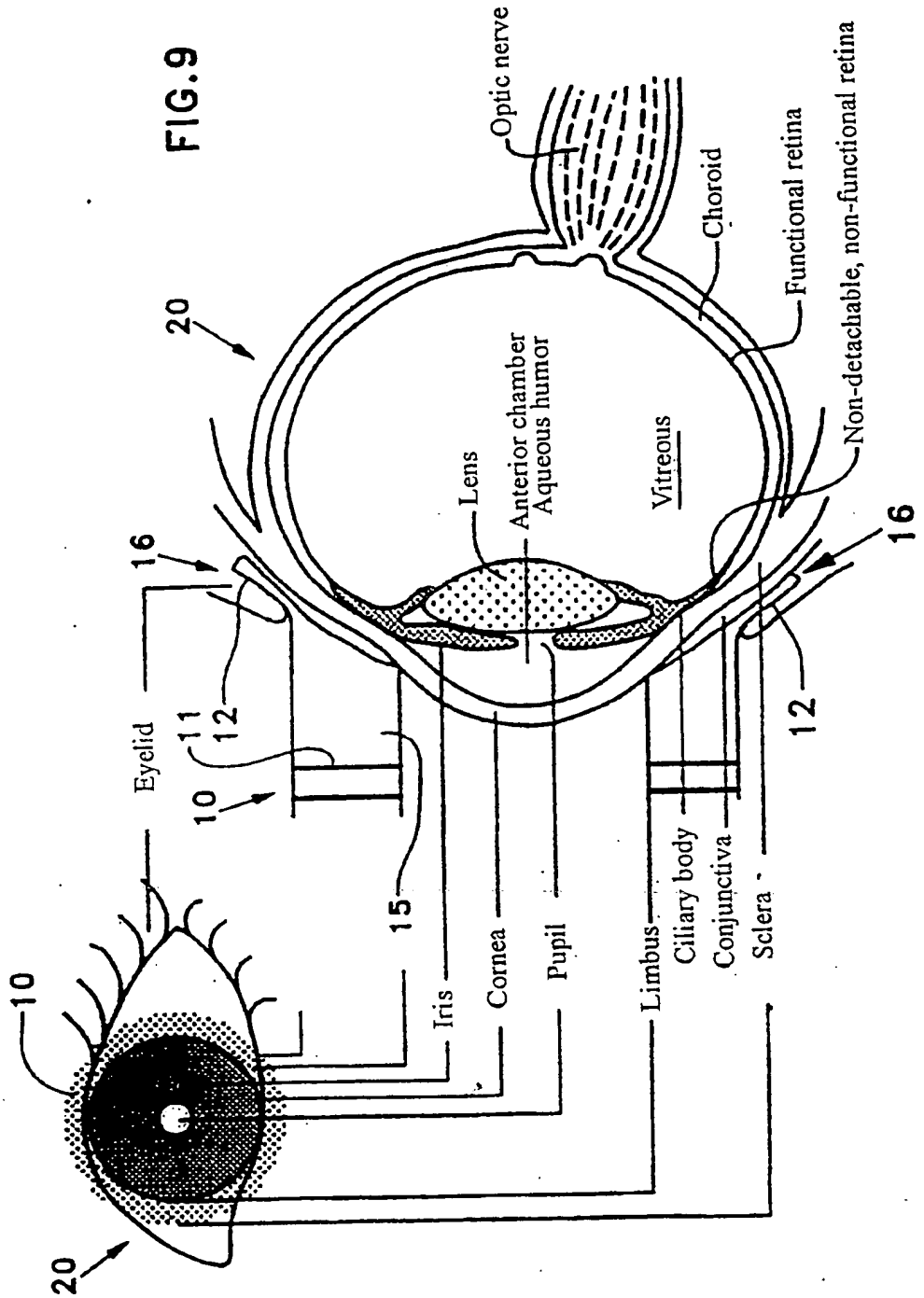

1000
800
600
400
200
0
µg/g of dry tissue extract
µg/ml of ocular medium
AH
V
C
I/CC
RET/CH
2
6
24
T(h)

FIG.8b

FIG.9


Optic nerve
Choroid
Functional retina
Non-detachable, non-functional retina
20
Lens
Anterior chamber
Aqueous humor
Vitreous
16
16
Eyelid
11
12
10
12
15
Iris
Cornea
Pupil
Limbus
Ciliary body
Conjunctiva
Sclera
10
20